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10/823,784	04/14/2004	Karen Uhlmann	3035-101	4952

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EXAMINER	
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/823,784	UHLMANN ET AL.	
	Examiner	Art Unit	
	AMANDA SHAW	1634	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *16 December 2008*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-5,7-20 and 22-39* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-5, 7-20, and 22-39* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114.

Applicant's arguments filed on November 19, 2008 have been entered and are addressed herein. Claims 1-5, 7-20, and 22-39 are currently pending and none of the claims have been amended. **THIS ACTION IS MADE FINAL even though it is a first action after the filing of a request for continued examination and the submission under 37 CFR 1.114. See MPEP § 706.07(b).**

Claim Rejections - 35 USC § 103

2. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein

were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

As noted in the MPEP 211.02, “a preamble is generally not accorded any patentable weight where it merely recites the purpose of a process or the intended use of a structure, and where the body of the claim does not depend on the preamble for completeness but, instead, the process steps or structural limitations are able to stand alone.” Further, in *Pitney Bowes Inc. v. Hewlett-Packard Co.*, 182F.3d 1298, 1305, 51 USPQ2d 1161, 1166 (Fed Cir. 1999) the court held that if the body of the claim sets forth the complete invention, and the preamble is not necessary to give “life, meaning and vitality” to the claim, “then the preamble is of no significance to claim construction because it cannot be said to constitute or explain a claim limitation.” In the present situation, the steps present in the method are able to stand-alone and the preamble limitation is not accorded patentable weight. Accordingly, the claim language of "a method for the diagnosis of a pathological condition or the predisposition for a pathological condition” in claim 12 and “a method for generating new nucleotide pairing partners upon amplification of at least one nucleic acid molecule for the detection of the methylation status of nucleotides of said nucleic acid molecule” in claim 32 merely sets forth the intended use or purpose of the claimed method, but does not limit the scope of the claims.

3. Claims 1-5, 7-9, 11-12, 19-20, 22-24, 26-33, and 36 are rejected under 35 U.S.C. 103(a) as being unpatentable over Uhlmann et al (Electrophoresis 1999) in view of Nyren et al (U.S. Patent 6258568 Issued 2001).

Regarding Claims 1, 7, 9, 12, 22, 24, 27, 31-33, and 36 Uhlmann teaches a method for identifying methylated cytosines comprising treating a sample containing genomic DNA derived from blood and tumor tissue with sodium bisulfite and amplifying the sample by PCR. Uhlmann et al further teach that the amplified nucleic acids were then cloned and plasmid DNA of the clones was prepared and sequenced using the dideoxynucleotide chain termination method determine the methylation state of the amplified product (Page 1750-1751). Thus Uhlmann teaches treating a nucleic acid sample with an agent suitable for the conversion of a nucleotide if present in methylated or non methylated form to pair with a nucleotide normally not pairing with the nucleotide prior to conversion, and amplifying the nucleic acid, sequencing the nucleic acid, and detecting whether said nucleotide is methylated. It is noted that the phrase in claim 12 "to diagnose said pathological condition or the predisposition for said pathological condition" is an intend use and does not limit the method steps. Even if the claims were amended to actually require a "diagnosing" step they would still be rejected because Uhlmann teaches an association between hypomethylation and pilocytic astrocytomas.

Uhlmann does not teach a method wherein the amplification primer has a label that forms an anchor for removal of single stranded amplified nucleic acid molecules. Uhlmann does not teach a method wherein said amplification primer is labeled with a

biotin. Further Uhlmann does not teach that the amplified nucleic acids were sequenced using a real-time sequencing method that comprises hybridizing a sequencing primer to a single stranded nucleic acid, adding a DNA polymerase, a ATP sulfurylase, a luciferase, an apyrase, adenosine phosphosulfate (APS), and luciferin, sequentially adding each dNTP, and detecting a luminescent signal. Further Uhlmann does not teach a sequencing method that is a high throughput method.

However Nyren teaches an alternative method for sequencing. The method of Nyren PCR is performed using one or more primers that carry a functional group such as a biotin which permits subsequent immobilization and aids in the separation of a single stranded DNA (Col 8, lines 1-5). Thus Nyren teaches a method wherein the amplification primer has a label that forms an anchor for removal of single stranded amplified nucleic acid molecules. Nyren further teaches a real time sequencing method called pyrosequencing that can be used to identify a base at a predetermined position in a DNA sample using an extension primer, which hybridizes immediately adjacent to the target position. The DNA sample and extension primer are mixed with a DNA polymerase, a ATP sulfurylase, a luciferase, a apyrase, a adenosine phosphosulfate and luciferin. Then dNTPs are successively added to the same sample primer mixture and the dNTPs will only become incorporated and release pyrophosphate (PPi) if it is complementary to the base in the target position. When the PPi is released a certain amount of light gets released that is equivalent to the amount of incorporated nucleotides. The unincorporated dNTPs get degraded (Column 2, lines 25-42). Thus Nyren teaches a method wherein the amplified nucleic acids are sequenced using a

high throughput real-time sequencing method. It is a property of the method of Nyren that the identity of more than one nucleotide is determined. Nyren also teaches that pyrosequencing can be used to detect disease.

Accordingly, it would have been obvious to one of ordinary skill in the art at the time the invention was made to have modified the method of Uhlmann by using the sequencing method of Nyren which includes performing PCR with at least one amplification primer labeled with a biotin and then sequencing the single stranded nucleic acid via pyrosequencing. Specifically Nyren teaches that amplification primer with labels that form anchors are useful for the removal of single stranded amplified nucleic acid molecules. Further Nyren et al teaches that the benefit of performing pyrosequencing over other sequencing methods such as the enzymatic chain termination method of Sanger is that pyrosequencing enables a base to be identified in a target position and DNA to be sequenced simply and rapidly while avoiding the need for electrophoresis and use of harmful radiolabels (Column 1, lines 60-64). Nyren further teach that other sequencing methods which rely on electrophoresis are not well suited for large-scale genome projects or clinical sequencing where high throughput is needed (Column 1, lines 15-30). However the pyrosequencing method of Nyren opens up the possibility for an automated approach for large scale, non-electrophoretic sequencing procedures which allow for continuous measurement of the progress of the polymerization reaction with time. The method of Nyren also has the advantage that multiple samples may be handled in parallel (Column 9, lines 4-6). Further the claimed method is obvious because the substitution of the PCR, cloning, and sequencing steps

performed by Uhlmann for the PCR and sequencing steps performed by Nyren would have yielded predictable results to one or ordinary skill in the art at the time of the invention.

Regarding Claims 2-4, 19, and 28-29 Uhlmann teaches a method wherein the nucleic acid sample is genomic DNA derived from peripheral blood lymphocytes and from tumor tissue (page 1749, col 1). Thus Uhlmann teaches a method wherein the sample DNA is derived from a tumor tissue and a body fluid.

Regarding Claims 5 and 20 Uhlmann teaches a method wherein the nucleic acid is amplified via PCR (page 1749, col 1).

Regarding Claims 8, 11, 23, 26, and 30 Uhlmann teaches a method wherein non methylated cytosines are converted to uracil via sodium bisulfite treatment (page 1749, col 1). Thus Uhlmann teaches a method wherein the nucleotide of (a) is a cytosine and is part of a CpG. Upon bisulfite treatment the methylated cytosines are converted to uracils so that they pair with an adenosine instead of a guanine.

4. Claims 12-16, 18 and 38 are rejected under 35 U.S.C. 103(a) as being unpatentable over Uhlmann et al (Electrophoresis 1999) in view of Nyren et al (U.S. Patent 6258568 Issued 2001) and in further view of Herman (U.S. Patent 5786146 Issued 1998).

The teachings of Uhlmann et al and Nyren et al are presented above.

The combined references do not teach that the methylation status is used to diagnose a pathological condition such as cancer, a neurodegenerative disease or another neurological disorder. The combined references also do not teach that the methylation status is used diagnose cancer that is a primary tumor, a metastasis or a residual tumor. The combined references do not teach that the primary tumor is a glioma selected from the group comprising: astrocytoma, oligodendroglioma, an oligoastrocytoma, a glioblastoma, and a pilocytic astrocytoma. The combined references also do not teach that the neurological disorder is selected from the group comprising: Prader-Willi-Syndrome, Angelman-Syndrome, Fragile-X-Syndrome, or ATR-X-Syndrome.

However, Herman et al teaches that the detection of methylated CpG containing nucleic acid is indicative of several disorders. Such disorders include but are not limited to low grade astrocytoma, anaplastic astrocytoma, glioblastoma, medulloblastoma, colon cancer, lung cancer, renal cancer, leukemia, breast cancer, prostate cancer, endometrial cancer and neuroblastoma. Identification of methylated CpG status is also useful for detection and diagnosis of genomic imprinting, fragile X syndrome and X-chromosome inactivation (Column 10, lines 49-58).

Accordingly it would have been obvious to one of ordinary skill in the art at the time the invention was made to have applied the method of Uhlmann and Nyren to diagnose the pathological disorders that Herman teaches that are associated with methylation. It was well known in the art at the time the invention was made that the detection of methylated sequences is indicative of several pathological disorders.

Accordingly, one of ordinary skill in the art would have been motivated to use the method of Uhlmann and Nyren in order to have achieved the advantage of being able to diagnose these diseases.

5. Claim 17 is rejected under 35 U.S.C. 103(a) as being unpatentable over Uhlmann et al ((Electrophoresis 1999) in view of Nyren et al (U.S. Patent 6258568) and Herman (U.S. Patent 5786146 Issued 1998) as applied to claims 12 and 38 above, and in further view of Feinberg (Pub No. US 2003/0232351).

The teachings of Uhlmann, Nyren, and Herman are presented above.

The combined references do not teach a method used to diagnose neurodegenerative diseases such as Alzheimer's disease, Parkinson disease, Huntington disease, or Rett-Syndrome.

However, Feinberg teaches a method of determining a disease state in a subject by determining DNA methylation status. Although the disease state is often cancer, the methods taught by Feinberg also include Alzheimer's disease and Parkinson's disease (Paragraph 0029).

Accordingly it would have been obvious to one of ordinary skill in the art at the time the invention was made to have applied the method of Uhlmann, Nyren and Herman used to diagnose primary tumors, to also diagnose neurodegenerative diseases. It was well known in the art at the time the invention was made that the detection of methylated sequences is indicative of certain neurodegenerative diseases.

Accordingly, one of ordinary skill in the art would have been motivated to use the method of Uhlmann, Nyren and Herman in order to have achieved the advantage of being able to diagnose these diseases.

6. Claims 10, 25, 34, and 39 are rejected under 35 U.S.C. 103(a) as being unpatentable over Uhlmann et al ((Electrophoresis 1999) in view of Nyren et al (U.S. Patent 6258568) as applied to claims 1 and 12 above, and in further view of Sylvan (US Patent 7078168 Filed 2/2002).

The teachings of Uhlmann and Nyren are presented above.

The combined references do not teach a method further comprising calculating a frequency of methylated nucleotides from the results of said real time sequencing. Further the combined references do not teach a method wherein an allele frequency of 5% can be detected or a method wherein an allele frequency of 5% with a standard deviation of not more than 1% is detected. In the instant case the allele frequency is being interpreted as a range of 4%-6%.

However, Sylvan teaches a method of determining the frequency of an allele in a population of nucleic acid molecules. The method comprises performing primer extension reactions using a primer which binds at a predetermined site located in nucleic acid molecules and obtaining a pattern of nucleotide incorporation (Abstract). Specifically Figs 4a-c and Fig 6-7 depicts graphically relative peak heights from a pyrosequencing reaction plotted against allele frequency. As you can see an allele frequency was detected. The wherein clause in claim 34 is conditional in view of the

"can be" language. Therefore the claims actually only require detecting an allele frequency. Regarding claim 39, Sylvan does not exemplify a method wherein an allele frequency of 5% was detected with a standard deviation of not more than 1%, however Sylvan teaches that for SNPs SNPE1.5, SNPE7.5 and SNPE4.5 (See Figs 4a-c) it is expected that allele frequencies of 5% with a standard deviation of not more than 1% can be detected. Therefore even if the expected results do not end up being equivalent to the obtained results, it would be obvious to modify the method in order to determine an allele frequency of 5% with a standard deviation of not more than 1%.

Accordingly it would have been obvious to one of ordinary skill in the art at the time the invention was made to have modified the method of Uhlmann and Nyren by further calculating the frequency of methylated nucleotides from the results of the pyrosequencing as suggested by Sylvan. The method of Sylvan is advantageous in that it determines the exact sequence of a nucleic acid fragment while directly measuring the amount of nucleotide incorporated. Using this method is it possible to obtain accurate, cost effective, and rapid information on allele frequencies (Column 22, lines 39-67 and Column 23, lines 1-4).

7. Claim 35 is rejected under 35 U.S.C. 103(a) as being unpatentable over Uhlmann et al ((Electrophoresis 1999) in view of Nyren et al (U.S. Patent 6258568) as applied to claim 1 above, and in further view of Laird (US 2002/0086324 Filed 10/2001).

The teachings of Uhlmann and Nyren are presented above.

The combined references do not teach a method wherein the amplification primer does not comprise CpG.

However, Laird teaches a method wherein a genomic DNA is provided that has mixed methylation status. The sample is converted in a standard sodium bisulfite reaction and the mixed products are amplified by a PCR reaction using primers that do not overlap any CpG dinucleotides. This produces an unbiased (with respect to methylation status) heterogeneous pool of PCR products. The mixed or heterogeneous pool can then be analyzed by a technique capable of detecting sequence differences (Para 0037).

Accordingly it would have been obvious to one of ordinary skill in the art at the time the invention was made to have modified the method of Uhlmann and Nyren by using an amplification primer that does not contain CpGs as suggested by Laird. The method of Laird is advantageous because primers that lack CpG dinucleotides can be used to amplify the sequence between the two primers, regardless of the DNA methylation status of that sequence in the original genomic DNA (Para 0016).

8. Claim 37 is rejected under 35 U.S.C. 103(a) as being unpatentable over Uhlmann et al ((Electrophoresis 1999) in view of Nyren et al (U.S. Patent 6258568) as applied to claims 1 and 8 above, and in further view of Hyman (US 5602000 1997).

The teachings of Uhlmann and Nyren are presented above.

The combined references do not teach a method wherein said nucleotide of claim 1 step (a)(i) is an adenine.

However Hyman teaches a method wherein adenine is converted to hypoxanthine to give rise to a nucleotide pairing with cytosine (Example 19).

Accordingly it would have been obvious to one of ordinary skill in the art at the time the invention was made to have modified the method of Uhlmann and Nyren by converting adenine to hypoxanthine to give rise to a nucleotide pairing with cytosine as suggested by Hyman. Methods of converting adenine to hypoxanthine were well known in the art at the time of the invention as demonstrated by Hyman and thus one could have combined the methods of Uhlmann, Nyren, and Hyman and the results would have been predictable to one of skill at the time of the invention.

Response To Arguments

9. In the response filed November 19, 2008 the Applicants continued to traverse the rejections made under 35 USC 103(a) over Uhlmann (Electrophoresis 1999) in view of Nyren (US Patent 6258568).

First the Applicants argue that a person skilled in the art would be reluctant to make the modification to Uhlmann that the Office suggested, namely detectably labeling Uhlmann's amplification primers because it would interfere with Uhlmann's subsequent cloning step. Further the Applicants argue that the modification proposed by the Office would render Uhlmann unsatisfactory for its intended purpose. The Applicants refer to

MPEP 2143.01 and In re Gordon 733 F. 2d 900, 221 USPQ 1125 (Fed. Cir. 1984) for support. Additionally they refer to In re Ratti, 270 F.2d 810, 813 (CCPA 1959) and argue that the Examiners analysis changes the basic principles under which Uhlmann was designed to operate.

This argument has been fully considered but is not persuasive. Uhlmann is directed to analyzing changes in methylation patterns between tumor DNA and non tumor DNA which is accomplished by treating genomic DNA with sodium bisulfite and amplifying the sample by PCR. Then the amplified nucleic acids are cloned and plasmid DNA from the clones is sequenced using the dideoxynucleotide chain termination method to determine the methylation state of the amplified product (Page 1750-1751). Modifying Uhlmann by performing PCR using at least one amplification primer that is detectably labeled with biotin and then directly sequencing the PCR products via pyrosequencing as suggested by Nyren would not require cloning or any other subsequent steps to detect methylation. Therefore the issue of Uhlmann being inoperable is not relevant. Applicants are reminded that the modification of Uhlmann is **NOT** just the use of the biotinylated PCR primer. The Applicants arguments keep focusing only on the biotinylated primer and they keep overlooking the subsequent steps of Nyren. In the instant case the modification of Uhlmann is the use of the biotinylated PCR primer **and** pyrosequencing which replaces the PCR, cloning, and dideoxy sequencing steps of Uhlmann. The Applicants should recognize that it is not that one step of Uhlmann is being modified (i.e. the PCR step with the biotinylated primer) and then the rest of Uhlmann is being carried out. In actuality the PCR, cloning,

and dideoxy sequencing steps of Uhlmann are being replaced by the PCR and pyrosequencing steps of Nyren. The modified method of Uhlmann in view of Nyren will comprise treating a sample with bisulfite (Uhlmann), performing PCR using a biotinylated primer (Nyren), and pyrosequencing (Nyren).

Next the Applicants argue that the combination of Uhlmann and Nyren would render the reaction mixture more complex, leading to potential technical difficulties. Further they state that Uhlmann does not provide any motivation for the combination that the Office has made.

This argument has been considered but is not persuasive. In the instant case the combination of Uhlmann and Nyren is not any more complex than Uhlmann itself, rather the combination is a simpler method because it eliminates the electrophoresis, cloning, and dideoxy sequencing steps of Uhlmann. Contrary to the assertion that there is no motivation to combine Uhlmann and Nyren, it is noted that Nyren teaches several benefits of pyrosequencing. For example Nyren specifically teaches that the benefit of performing pyrosequencing over other sequencing methods such as the enzymatic chain termination method of Sanger is that pyrosequencing enables a base to be identified in a target position and DNA to be sequenced simply and rapidly while avoiding the need for electrophoresis and use of harmful radiolabels (Column 1, lines 60-64). Nyren further teach that other sequencing methods which rely on electrophoresis are not well suited for large-scale genome projects or clinical sequencing where high throughput is needed (Column 1, lines 15-30). However the pyrosequencing method of Nyren opens up the possibility for an automated approach

for large scale, non-electrophoretic sequencing procedures which allow for continuous measurement of the progress of the polymerization reaction with time. The method of Nyren also has the advantage that multiple samples may be handled in parallel (Column 9, lines 4-6). Thus motivation is present and has been provided by Nyren.

Next the Applicants point to a recent discussion of non-obviousness in Ortho-McNeil Pharmaceutical v. Mylan Labs, 2008-1223, Fed Cir. March 31, 2008. They note that in Ortho-McNeil the court specifically stated that the TSM test, flexibly applied merely assures that the obviousness test proceeds on the basis of evidence-teachings, suggestions, or motivations that arise before the time of invention as the statute requires. Applicants respectfully submit that the appropriate showing was not provided.

This argument has been considered but is not persuasive. Again it is reiterated that the prior art of Nyren teaches several benefits of pyrosequencing. Nyren specifically teaches that the benefit of performing pyrosequencing over other sequencing methods such as the enzymatic chain termination method of Sanger is that pyrosequencing enables a base to be identified in a target position and DNA to be sequenced simply and rapidly while avoiding the need for electrophoresis and use of harmful radiolabels (Column 1, lines 60-64). Nyren further teach that other sequencing methods which rely on electrophoresis are not well suited for large-scale genome projects or clinical sequencing where high throughput is needed (Column 1, lines 15-30). However the pyrosequencing method of Nyren opens up the possibility for an automated approach for large scale, non-electrophoretic sequencing procedures which allow for continuous measurement of the progress of the polymerization reaction with

time. The method of Nyren also has the advantage that multiple samples may be handled in parallel (Column 9, lines 4-6). Thus motivation to replace the PCR, electrophoresis, cloning, and dideoxy sequencing steps of Uhlmann for the PCR and pyrosequencing steps of Nyren has been provided. Further since Uhlmann and Nyren both teach methods for sequencing nucleic acids, an artisan of ordinary skill would have found it obvious to combine these teachings since they both pertain to sequencing.

Regarding Claim 12, the Applicants continue to argue that step (d) requires diagnosing a pathological condition or the predisposition for a pathological condition. They further state that the Office has not explained how, subsequent to the suggested modification of Uhlmann the recited detection may take place.

This argument has been considered but is not persuasive. First of all the claims do not have an active process step of "diagnosing". The only actual step required in (d) is "detecting whether said nucleotide is methylated or not methylated". The combined references teach all of the active process steps required by the claims. Further it is noted that the modification Uhlmann in view of Nyren does not change the other teachings of Uhlmann which state methylated DNA is associated with disease. Again it is noted that the combination of Uhlmann and Nyren only changes how the sequence of a nucleic acid is determined. It does not change the relationship between methylation and disease. Even if the claims were amended to actually require an active process step of “diagnosing" they would still be rejected because Uhlmann teaches an association between hypomethylation and pilocytic astrocytomas and Nyren teaches pyrosequencing can be used to detect disease.

Regarding Claims 34 and 39 the Applicants state that the Office concedes that Sylvan only teaches that there is an expectation that an allele frequency of 5% with a standard deviation of not more than 1% is detected, but suggests that, even if the expected results do not end up being equivalent to the [claimed] results, it would have been obvious to modify the method in order to determine the recited allele frequency. However the Applicants argue that the Office has not provided any indication how the reference is to be modified to accomplish this.

This argument has been considered but is not persuasive. First of all the pyrosequencing method of Nyren and Sylvan comprises all of the same pyrosequencing steps that are taught in the instant specification. Since the steps are all identical it is expected that any pyrosequencing method could achieve an allele frequency of 5% with a standard deviation of not more than 1%. Further as discussed in MPEP 2144.05(b), "(w)here the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation. As such it would be obvious to optimize pyrosequencing and one of skill in the art would have a reasonable expectation of success since there are no differences between the pyrosequencing method of instant invention and the pyrosequencing method disclosed in the prior art.

For these reasons the rejections made under 35 USC 103(a) are maintained.

Conclusion

10. All claims are drawn to the same invention claimed in the application prior to the entry of the submission under 37 CFR 1.114 and could have been finally rejected on the grounds and art of record in the next Office action if they had been entered in the application prior to entry under 37 CFR 1.114. Accordingly, **THIS ACTION IS MADE FINAL** even though it is a first action after the filing of a request for continued examination and the submission under 37 CFR 1.114. See MPEP § 706.07(b). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to AMANDA SHAW whose telephone number is (571)272-8668. The examiner can normally be reached on Mon-Thurs 8:00 TO 6:30. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ram Shukla can be reached at 571-272-0735. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Amanda M. Shaw
Examiner
Art Unit 1634

/Ram R. Shukla/
Supervisory Patent Examiner, Art Unit 1634